Low-Dose Recombinant Factor VIIa in the Management of Uncontrolled Postoperative Hemorrhage in Cardiac Surgery Patients

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RECOMBINANT FACTOR VIIa (rFVIIa) is increasingly being used for off-label treatment of major hemorrhage in patients without hemophilia.[1-5] At present, only a few small randomized trials have been published concerning safety, efficacy, and optimal dosing strategies of rFVIIa for these off-label treatments.[6] Its use in cardiac surgery has been described in case reports only. The dosages described in cardiac surgical patients without hemophilia are predominantly 90 μg/kg,[5,7-12] comparable with the official dosage for patients with inherited or acquired hemophilia.[13] This article reports a series of 7 consecutive patients, of whom 4 were treated successfully with very low doses of rFVIIa (40 μg/kg or less) for uncontrolled bleeding after cardiac surgery. All 7 patients stopped bleeding after rFVIIa.

PATIENTS

In this teaching hospital, approximately 1750 patients undergo cardiac surgery with cardiopulmonary bypass (CPB) each year, including 225 (13%) ascending aorta and or aortic arch reconstructions. Cell savers are used in all cardiac surgery patients to salvage the patients' red blood cells, resulting in fewer than 50% of patients requiring transfusion of homologous red blood cells. However, in some patients no acceptable hemostasis can be achieved despite reversal of heparin therapy and transfusion of blood products. When blood products and antifibrinolytic agents (tranexamic acid or aprotinin) had been given and other correctable causes such as hypothermia and acidosis were corrected, the authors considered administration of rFVIIa in an attempt to control hemorrhage.

Between January 2004 and December 2004, 7 of 1752 patients (0.4%) undergoing cardiac surgery with CPB were treated with rFVIIa because of uncontrolled postoperative bleeding. Patient characteristics, type of surgery, dosage of rFVIIa, judgment of effect of rFVIIa, and outcome are summarized in Table 1. The amount of cell salvaged blood, prothrombin time (international normalized ratio; PT-INR), activated partial prothrombin time (Cephotest), platelet count, need for transfusion before and after administration of rFVIIa, temperature at rFVIIa administration, use of additional hemostatic drugs, and postoperative chest tube production are shown in Table 2. The clinical efficacy of rFVIIa on hemostasis was judged successful or unsuccessful. A sufficient reduction in the amount of blood loss, enabling sternal closure and transportation to the intensive care unit without further use of the cell saver, was considered success.

All patients except the last one received 1 dose of rFVIIa, with individual doses varying from 26 to 111 μg/kg. In all cases, rFVIIa was administered after termination of CPB and after a minimum of 1 hour of attempting to control bleeding with conservative methods. The first and second treated patients received 1 dose of 9.6 mg (111 μg/kg) and 4.8 mg (63 μg/kg) of rFVIIa, respectively. The next 4 patients received 1 dose of 2.4 mg (26-40 μg/kg) of rFVIIa. The seventh patient received 2.4 mg (25 μg/kg) of rFVIIa, followed by another 2.4 mg (25 μg/kg) after 20 minutes. In all patients bleeding markedly decreased after administration of rFVIIa, enabling termination of the surgical procedure. No patients required a repeat operation to treat early tamponade or bleeding. Six patients were discharged from the hospital alive, and 1 patient died of intestinal ischemia on the first postoperative day.

After carefully reevaluating all patients, it was concluded that none of these cardiac surgery patients had preexisting coagulopathy and all surgical options to control bleeding had been tried. At rFVIIa administration all relevant correctable causes of uncontrolled hemorrhage were corrected insofar as possible. Heparin treatment was reversed with protamine (1:1) in all patients, and antifibrinolytic agents were used in 6 patients. Antifibrinolytic agents are not used prophylactively in this hospital, because of conflicting evidence in the literature. As for concomitant medications, 3 of the 7 patients used warfarin sodium (Coumadin) as an anticoagulation drug preoperatively, but they had acceptable preoperative PT-INR values. One of these 3 patients also used aspirin, which was discontinued preoperatively.

DISCUSSION

Massive blood transfusion during surgery contributes to a higher risk for complications and death.[14] The use of rFVIIa in cardiac surgical patients with uncontrolled bleeding can minimize the need for further transfusion and reduce the risk for complications. Furthermore, the balance in these patients between bleeding and thromboembolic complications is extremely delicate. Many cardiac patients have vulnerable atherosclerotic plaques in their vasculature; excessive thrombin generation by rFVIIa may therefore increase the incidence of complications resulting from thromboembolic processes. At this time, no randomized placebo-controlled studies are available on the effective and safe dosage of rFVIIa in cardiac surgical patients.

The current report is a series of 7 consecutive cardiac surgical patients treated with different doses of rFVIIa. The reason varying doses of rFVIIa were given was to seek the lowest dose that was effective to achieve adequate hemostasis. Furthermore, low doses were used because of the risk for side effects such as thromboembolic complications, and the cost of using the drug. In all patients, the reason for treatment with rFVIIa was uncontrolled bleeding at the time, as judged by the surgeon and anesthesiologist.

Use of rFVIIa successfully stopped bleeding in all 7 patients, enabling sternal closure and termination of the surgical procedure. In no patients were thromboembolic events observed, and no patients required further blood transfusion in the operating room after rFVIIa administration. When comparing the different doses of rFVIIa administered, no differences in clinical efficacy were observed. In 4 patients a dose of 26-40 μg/kg

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Table 1. Patient Characteristics and Results of rFVIIa Treatment in 7 Patients With Uncontrolled Postoperative Hemorrhage after Cardiac Surgery

Patient	Age (y)	Sex	Type of Surgery	rFVIIa Dosage	Effect	Length of Stay (d)		Discharge Location
						Intensive Care Unit	Ward	
1	46	Male	Type A dissection, aortic arch, aortic valve replacement, CABG	9.6 mg (111 μg/kg)	Bleeding stopped	35	8	Other hospital
2	76	Female	Aortic valve replacement	4.8 mg (63 μg/kg)	Bleeding markedly decreased	16	22	Nursing home
3	63	Male	Aortic arch replacement	2.4 mg (33 μg/kg)	Bleeding markedly decreased	1	0	*
4	80	Male	Repeat aortic valve replacement, CABG	2.4 mg (34 μg/kg)	Bleeding markedly decreased	2	4	Other hospital
5	45	Female	Aortic arch replacement with elephant trunk	2.4 mg (40 μg/kg)	Bleeding stopped	4	5	Other hospital
6	32	Male	Type A dissection, ascending aorta replacement	2.4 mg (26 μg/kg)	Bleeding stopped	4	8	Home
7	59	Male	CABG, aortic valve replacement, and ascending aorta replacement	4.8 mg (50 μg/kg)	Bleeding stopped	2	5	Home

Abbreviation: CABG, coronary artery bypass grafting.

*Patient died of intestinal ischemia; autopsy showed no thromboembolic events.

showed comparable clinical results as in the other patients who received higher doses. These findings confirm the results of Al Douri et al[8] describing a series of 5 patients with severe uncontrolled bleeding after heart valve replacement who were all effectively treated with a single dose of 30 μg/kg of rFVIIa. The authors realize that use of rFVIIa in the present patients did

Table 2. Clinical Data for 7 Patients With Uncontrolled Postoperative Hemorrhage after Cardiac Surgery

Patient	PT-INR*	Cell Saver Blood (mL)	Transfusion (U) Before rFVIIa	Other Hemostatics	PT-INR†	Cephotest†	Temperature‡ (°C)	Hb level† (mmol/L)	Platelet count† ($\times 10^9$/L)	Transfusion after rFVIIa (24 h) (U)	Postoperative drain production (24 h) (mL)
1§	1.0	6000	1 PC 3 FFP 2 P	2 g tranexamic acid	1.0	1.5	36.0	6.2	51	None	600
2§	1.0	960	5 PC 3 FFP 2 P	2 g tranexamic acid	1.3	1.2	36.3	5.5	194	None	900
3	1.5	5750	10 PC 10 FFP 2 P	2 g tranexamic acid	1.5	2.4	35.0	6.4	28	1 PC	1700
4§	1.2	1871	3 PC 2 FFP 1 P	–	1.0	1.9	34.8	3.7	34	None	1350
5	1.4	4070	4 PC 6 FFP 2 P	1 g tranexamic acid, 500,000 IU aprotinin	1.0	2.5	37.0	5.2	119	None	850
6	1.1	3400	2 PC 4 FFP 1 P	1 g tranexamic acid, 500,000 IU aprotinin	1.2	2.8	36.0	4.6	55	2 PC	780
7	1.0	2000	3 PC 5 FFP 1 P	1 g tranexamic acid	1.0	1.5	35.5	5.5	85	1 PC	550

Abbreviations: PT-INR, prothrombin time (international ratio); rFVIIa, recombinant factor VIIa; Hb, hemoglobin; PC, packed red blood cells; FFP, fresh frozen plasma; P, platelets.

*Preoperative PT-INR.

†Coagulation profile was not screened routinely before administration of rFVIIa in all patients. For patients with §, data presented are before administration of rFVIIa (35-77 min); for other patients, data presented are after administration of rFVIIa.

‡At rFVIIa administration.

not follow a strict protocol, and the patients were not screened with a coagulation profile before rFVIIa administration. However, most coagulation tests, except for thromboelastography, cannot reliably predict hemostatic function in patients with major bleeding, owing to the delay between sampling and test results. None of the patients had a record of preexisting coagulopathy.

In summary, administration of rFVIIa was effective in achieving hemostasis in these cardiac surgical patients. The doses of rFVIIa described in other reports were predominantly 90 μg/kg. In the present patients a low dose of $\leq$40 μg/kg seemed as effective as the higher doses. Inasmuch as no dose-response relationship has been described for rFVIIa in cardiac surgical patients, an initial dose of about 30 μg/kg is suggested to control life-threatening bleeding. When this dose is not effective in 10 to 30 minutes, an additional dose of 30 μg/kg should be given. This proposed strategy was confirmed in the seventh patient, who responded successfully after administration of a second dose of rFVIIa 20 minutes after the first dose. Larger prospective studies are needed to confirm these results and to assess the lowest effective and safe doses of rFVIIa, especially with the increasing use of rFVIIa in cardiac surgical patients.

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